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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/300,959	04/27/1999	MAURIZIO ZANETTI	P-ZA-3519	5037

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EXAMINER
BECKERLEG, ANNE M

ART UNIT	PAPER NUMBER
1632	17

DATE MAILED: 05/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/300,959	ZANETTI, MAURIZIO	
	Examiner	Art Unit	
	Anne M Beckerleg	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29 and 31-34* is/are pending in the application.

4a) Of the above claim(s) *1,2,5-17,22-28 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,18-21,29,31,32 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment received on 2/12/02 has been entered. Claim 30 has been canceled. New claim 35 has been added. Claims 1-29, and 31-34 are pending in the instant application. Of these, claims 1-2, 5-17, 22-28 and 33 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8. Claims 3-4 18-21, 29, 31-32, and 34-35 are currently under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action, can be found in the previous office actions.

Claim Rejections - 35 USC § 112

The rejection of original, amended, and new claims 3-4 18-21, 29, 31-32, and 34-35 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained in part. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the following instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the specification provides sufficient guidance for B cell specific expression elements other than the immunoglobulin enhancer/promoter. In particular, the applicant points to pages 28 and 33 of the instant specification. Page 28 simply states that hematopoietic cell expression elements capable of allowing expression of a genetic element in a B cell can be used in the instant invention. Page 33 states that a B cell specific promoter and enhancer can be used in the disclosed plasmid vectors. Neither of these pages actually teaches or discloses the structural or physical characteristics of any nucleic acid sequence which can function as a B cell specific promoter or enhancer. As stated in the previous office action, the specification only discloses a single B cell specific expression element, the immunoglobulin heavy chain promoter/enhancer. It is noted that the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.
> Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997)

In the absence of any specific guidance from the specification as to the identities or physical characteristics of promoter and/or enhancer elements which are B cell specific, the skilled artisan would not have been able to predict without undue experimentation, the sequence of a B cell

specific expression element for use in the instant methods other than the immunoglobulin heavy chain promoter/enhancer.

The applicant further argues that the art recognized unpredictability of utilizing various types of expression vectors and different promoter for expression therapeutic amounts of a gene in vivo is not relevant to the instant claims because the specification provides several working examples of the instant invention. The specification's working examples have been discussed in detail in previous office actions. In short, the working examples provided are limited to the use of DNA plasmid vectors which utilize the immunoglobulin heavy chain promoter/enhancer. The applicant has not provided any compelling evidence or arguments that the skilled artisan at the time of filing would consider the use of any nucleic acid other than a plasmid DNA, or any promoter other than the heavy chain promoter, as predictable in applicant's methods. Based on the evidence of record (Verma et al., Eck et al., Deonarian et al., and Miller et al.) which teaches the unpredictability of vector and promoter selection such that therapeutic levels of gene expression are achieved in target cells *in vivo,* applicant's working examples which use DNA plasmid vectors and the immunoglobulin heavy chain promoter/enhancer do not provide sufficient enablement for applicant's broad claims. The applicant is reminded that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). Also, 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable

correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970).

In regards to routes of immunization other than intrasplenic injection and the unpredictability of targeting B cells in vivo, the applicant argues that the specification identifies other target tissues, such as lymph nodes. However, as previously noted, the cellular composition of the spleen versus gut associated lymph organs, or lymph nodes is very different in terms of the percentages of different antigen presenting cells and the types of antigen presenting cells present. While the specification demonstrates that direct injection of the spleen results in the generation of immune responses, the specification fails to provide any evidence that the administration of the nucleic acids to any other lymphoid tissue would result in comparable levels of antibody or T cell mediated responses. Further, while claims 3-4, 18-21, and 34 are limited to the administration to lymphoid tissue, claims 29-32 broadly recite the administration of the nucleic acid such that any hematopoietic cells are targeted. These claims read on the administration of the nucleic acid by any route of administration. The applicant argues that articles cited to support the unpredictability of targeting a vector to a particular cell type *in vivo* are not applicable to the instant claims since the specification teaches the direct administration of the vectors to the lymphoid tissue. However, claims 29-32 are not so limited. Furthermore, as discussed in the previous office action, the specification fails to provide guidance as to vectors useful for the instant methods other than plasmid vectors, or provide guidance for the targeted expression either *in vivo* or *ex vivo* of a gene in any hematopoietic cell such that the level of gene expression results in a therapeutic effect

on any condition. The cited articles support not only the unpredictability of targeted gene delivery, but the unpredictability of therapeutic gene expression *in vivo* using currently available expression vectors (Eck et al., Verma et al., Deonarian, and Miller et al.). Therefore, in view of the art recognized unpredictability of targeted gene expression *in vivo*, the lack of guidance provided by the specification for vectors suitable for targeting hematopoietic cells *in vivo*, the lack of working examples concerning methods of targeted delivery other than intrasplenic injection, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

In regards to the treatment of any and all conditions using the instant invention, the applicant argues that the specification provides evidence for the treatment of Influenza and *Plasmodium falciparum* malaria sporozoites and also for the generation of CTL which recognize MUC-1. The applicant's working examples, as noted above, are limited to the intrasplenic injection of DNA plasmids encoding an antigen under the transcriptional control of the immunoglobulin heavy chain promoter/enhancer. The applicant's treatment claims are extremely broad and read on the treatment of any condition in an individual, this includes autoimmune diseases, congenital defects, cancer, and any and all diseases related to infection with a pathogen. The applicant has not provided sufficient support in the specification for claims of this breadth. The art of record clearly teaches that unpredictability of treating diseases resulting from genetic defects, autoimmunity, and cancer using gene therapy. The applicant's working examples which are limited to a single vector/promoter combination, a single route of administration, and a viral or

parasitic antigen, do not overcome the art recognized unpredictability of treating any and all diseases using applicant's disclosed methods. Case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves. *In re Gardner* 166 USPQ 138 (CCPA) 1970.

In conclusion, the office has analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement in the instant. It is also noted that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Thus, in view of the art recognized unpredictability of achieving therapeutic levels of gene expression *in vivo* using any vector and promoter combination, the lack of guidance concerning the level and duration of gene expression of any gene from any transfected cell at any cellular location *in vivo* which correlates with any therapeutic effect on any disease or condition, and the breadth of the claims, it would have required undue experimentation to practice the instant invention as claimed.

The rejection of claims 32 and 34 under 35 U.S.C. 112, second paragraph, for indefiniteness is maintained over claim 34. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

Claim 34 has been amended to recite the method of claim 3 wherein the nucleic acid is administered to said lymphoid tissue and targeted to a cell ex vivo, wherein the cell is then administered to said individual. The previous office action indicated that it was unclear how lymphoid tissue could be targeted ex vivo, and that it appeared that applicants were attempting to claim administration of B cells modified ex vivo. Applicant's amendments have not clarified this issue. The instant claims as written, now appear to recite a two step method wherein a nucleic acid is administered directly to lymphoid tissue in vivo, and further is targeted to a cell ex vivo. However, as this type of two-step methodology is not disclosed in the specification, it is unclear whether applicant intends to claim such a two step method or whether the claims are intended to recite the targeting of cells ex vivo which are then administered to the lymphoid tissue in vivo. Clarification is requested.

Claim Rejections - 35 USC § 102

The rejection of claims 18-19 under 35 U.S.C. 102(b) over Banerji et al. is withdrawn in view of new grounds of rejection of the claims under 35 U.S.C. 102 presented below.

Claims 18-19 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Maxwell et al. (1991) Cancer Res., Vol. 51 (16), 4299-4304. The applicant claims a nucleic acid molecule comprising a B cell promoter and enhancer operatively linked to a nucleic acid sequence.

Maxwell et al. teaches a plasmid expression vector comprising the promoter and enhancer of either the immunoglobulin heavy chain or kappa light chain genes operatively linked to the gene for diphtheria toxin A-chain (Maxwell et al., page 4299, and page 4300, Figure 1). Maxwell et al. further teaches that the immunoglobulin promoters and enhancers are B cell specific expression elements, and that B cells transfected in vitro with said plasmid express the encoded diphtheria toxin gene (Maxwell et al., pages 4299-4300). Thus, by teaching all the elements of the claims as written, Maxwell et al. clearly anticipates the instant invention.

Claim Rejections - 35 USC § 103

The rejection of original, amended, or new claims 3-4, 18-19, 29-31, and 35 under 35 U.S.C. 103 over Hurpin et al. in view of Banerji et al. is withdrawn over claims 18-19, and maintained over claims 3-3, 29-31, and 35. Applicant's arguments have been fully considered but

have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that neither Hurpin et al. nor Banerji et al. provides sufficient motivation for modifying the vector taught by Hurpin et al. to include B cell specific expression elements. In particular, the applicant argues that no specific suggestion is found in Hurpin to target B cells in the spleen, and that no specific suggestion is found in Banerji to express heterologous epitopes in B cells. The applicant concludes that only the teachings of the instant specification provide motivation for combining a B cell expression element in the vector taught by Hurpin et al. and that such use of hindsight reasoning is improper.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The applicant is also reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed

invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, Banerji et al. supplements Hurpin et al. by teaching a plasmid encoding the β-globin gene operatively linked to the immunoglobulin enhancer which is a B cell specific expression element (Banerji et al., page 730, Figure 1, and page 732, Figure 2). Banerji et al. further provides motivation for using a B cell specific enhancer by teaching that use of the immunoglobulin heavy chain enhancer to express a heterologous gene, β-globin, results in two fold increase in the magnitude of β-globin expression compared to vectors which utilize the viral SV40 enhancer (Banerji et al., page 729, abstract). Please note that β-globin is a heterologous epitope. Thus, based on the increased magnitude of gene expression using the immunoglobulin promoter as taught by Banerji et al., and the large percentage of B cells in the spleen, it would have been *prima facie* obvious at the time of filing to substitute the immunoglobulin heavy chain transcriptional elements taught by Banerji et al. for the viral elements taught by Hurpin et al. in order to increase antigen expression in the spleen and thus increase resulting immune responses. Based on the successful generation of immune responses observed by Hurpin et al. using intrasplenic injection, and the activity of the immunoglobulin promoter observed by Banerji, the skilled artisan would have had a reasonable expectation of success in using the immunoglobulin heavy chain promoter/enhancer in the vectors and methods taught by Hurpin et al. The fact that

Hurpin et al. teaches that immune responses can be generated using viral expression elements does not contraindicate the use of an alternate expression element that has been demonstrated to be more potent than a viral expression element. The increased activity of the immunoglobulin enhancer element compared to a viral enhancer element as taught by Banerji et al. provides sufficient motivation for the skilled artisan to use the immunoglobulin enhancer over a viral enhancer. Furthermore, at the time of filing, B cells were well known to be professional antigen presenting cells. Thus, the large percentage of B cells, potent antigen presenting cells, in the spleen provides further motivation for utilizing a B cell specific expression element.

Therefore, for reasons of record as discussed in detail above, the rejection of claims 3-4, and 29-31 is maintained.

No claims are allowed.

ny inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Beckerleg

A.M.S. BECKERLEG
PATENT EXAMINER